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Safety and efficacy of nivolumab and standard chemotherapy drug combination in patients with advanced non-small-cell lung cancer: a four arms phase Ib study

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Background: The human IgG4 monoclonal antibody nivolumab targets programmed cell death-1 (PD-1) and promotes antitumor response by blocking the interaction of PD-1 with its ligands. This single-center phase Ib study investigated the tolerability, safety, and pharmacokinetics of nivolumab combined with standard chemotherapy in patients with advanced non-small-cell lung cancer (NSCLC).

Patients and methods: Patients who had stage IIIB without indication for definitive radiotherapy, stage IV, or recurrent NSCLC were eligible. Regimens were nivolumab 10 mg/kg + gemcitabine/cisplatin (arm A), pemetrexed/cisplatin (arm B), paclitaxel/carboplatin/bevacizumab (arm C), or docetaxel (arm D). Regimens A, B, and D were repeated every 3 weeks for up to four cycles and regimen C was repeated for up to six cycles; nivolumab alone (arm A), with pemetrexed (arm B), bevacizumab (arm C), or docetaxel (arm D) was continued every 3 weeks as maintenance therapy until disease progression or unacceptable toxicity. Dose-limiting toxicity (DLT) was evaluated during the first treatment cycle.

Results: As of March 2014, six patients were enrolled in each arm. The combination of nivolumab 10 mg/kg and chemotherapy was well tolerated. DLT was observed in only one patient in arm A (alanine aminotransferase increased). Select adverse events (those with a potential immunologic cause) of any grade were observed in six, four, six, and five patients in arms A, B, C, and D, respectively. Three, three, six, and one patient achieved partial response while median progression-free survival was 6.28, 9.63 months, not reached, and 3.15 months in arms A, B, C, and D, respectively.

Conclusions: Combination of nivolumab 10 mg/kg and chemotherapy showed an acceptable toxicity profile and encouraging antitumor activity in patients with advanced NSCLC.

Clinical trials number: Japanese Pharmaceutical Information Center Clinical Trials Information (JapicCTI)-132071.

Key words: nivolumab, combination, chemotherapy, non-small-cell lung cancer

introduction

In advanced non-small-cell lung cancer (NSCLC), cytotoxic chemotherapy is still the mainstay of treatment, although molecular target therapies against epidermal growth factor receptor (*EGFR*) mutations and anaplastic lymphoma kinase (*ALK*) rearrangements have been developed. Platinum-based chemotherapy remains the standard first-line therapy [1, 2] and monotherapies such as docetaxel have been recommended as second-line therapies [3], but these efficacies are limited.

Nivolumab (ONO-4538, BMS-936558) is a human monoclonal IgG4 antibody targeting programmed cell death-1. A global phase I study enrolling ∼300 patients with advanced solid tumors (CA209-003 study) demonstrated the safety and potency of nivolumab [4]. The maximum tolerated dose was not reached at the doses tested in the study (1, 3, or 10 mg/kg administrated intravenously every 2 weeks). On the other hand, in a Japanese phase I study (ONO-4538-01) with advanced solid tumors, the tolerability of nivolumab was confirmed at a dose of ≤20 mg/kg every 2 weeks [5].

Two pivotal phase III studies demonstrated the remarkable safety and efficacy of nivolumab monotherapy as a second-line treatment in patients with advanced NSCLC [6, 7], and the

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combination use of nivolumab with standard chemotherapy, molecular target agent, or the other immune checkpoint inhibitor are highly anticipated. Preclinical data have shown that several cytotoxic agents may act as immunomodulators and may have a synergistic or cumulative effect with immune checkpoint inhibitors. Gemcitabine and docetaxel have the ability to eliminate immunosuppressive cells such as myeloid-derived suppressor cells (MDSC) [8, 9], and platinum agents induce immunogenic cell death and may also have antitumor immunological effects [10]. On the other hand, anti-vascular endothelial growth factor (VEGF) agents such as bevacizumab decreased immunosuppressive cytokines, inhibited the infiltration of immunosuppressive cells (MDSC, Treg, and macrophages) [11], and improve the delivery of cytotoxic agents, nivolumab, and lymphocytes into tumors [12].

Based on these preclinical rationales, we carried out a phase Ib study of combination therapy with nivolumab and standard chemotherapy in patients with advanced NSCLC. The study objectives were to assess the tolerability, safety, pharmacokinetics, and antitumor activity of the combination therapy on patients with advanced NSCLC.

materials and methods

patients

Patients who met the following criteria were eligible: had histologically or cytologically confirmed NSCLC; had chemotherapy-naïve NSCLC for arm A, chemotherapy-naïve non-squamous NSCLC for arm B and C, one prior chemotherapy including platinum-doublet or two prior chemotherapies including platinum-doublet, and an EGFR or ALK tyrosine kinase inhibitor for arm D; had stage IIIB without indication for definitive thoracic radiotherapy, stage IV, or recurrent NSCLC; age ≥20 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; had measurable lesions as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; had adequate hematological, hepatic, and renal function. Patients who had a history of infusion reaction with other antibody therapies, history of interstitial lung disease (ILD) or pulmonary fibrosis, coexisting autoimmune disease, who were receiving systemic corticosteroids or immune suppressants, who had symptomatic central nerve system metastasis were excluded.

treatment

This study was a single-center, open-label, phase Ib study. We evaluated the tolerability, safety, and estimated antitumor activity of the following four treatment regimens (arms A, B, C, and D): (A) nivolumab 10 mg/kg on day 1, gemcitabine 1250 mg/m^2 on days 1 and 8, and cisplatin 80 mg/m^2 on day 1, every 3 weeks for up to 4 cycles, followed by nivolumab 10 mg/kg on day 1 every 3 weeks until disease progression or unacceptable toxicity, as the first-line treatment for advanced NSCLC; (B) nivolumab 10 mg/kg on day 1, pemetrexed 500 mg/m^2 on day 1, and cisplatin 75 mg/m^2 on day 1 every 3 weeks for up to 4 cycles, followed by nivolumab 10 mg/kg on day 1 and pemetrexed 500 mg/m^2 on day 1 every 3 weeks, as the first-line treatment for advanced non-squamous NSCLC; (C) nivolumab 10 mg/kg on day 1, paclitaxel 200 mg/m^2 on day 1, carboplatin target AUC of 6.0 mg/ml/min on day 1, and bevacizumab 15 mg/kg on day 1 every 3 weeks for up to 6 cycles, followed by nivolumab 10 mg/kg on day 1 and bevacizumab 15 mg/kg on day 1 every 3 weeks, as the first-line treatment for advanced non-squamous NSCLC; (D) nivolumab 10 mg/kg on day 1 and docetaxel 75 mg/m^2 on day 1 until disease progression or unacceptable toxicity, as the second- or third-line treatment for advanced NSCLC. We administrated nivolumab 10 mg/kg every 3 weeks in this study, for a previous Japanese phase I study in patients with advanced solid tumors demonstrated the tolerability of nivolumab up to 20 mg/kg every 2 weeks [5] and pharmacokinetic modeling in an US phase I study showed that nivolumab 5 mg/kg every 3 weeks provides a steady-state trough concentration equivalent to nivolumab 3 mg/kg every 2 weeks [13].

Nivolumab was administered intravenously for 60 min before the other chemotherapeutic agents. In arm A, patients received 9.9 mg dexamethasone intravenously on day 1, 4 mg orally twice daily on days 2–4, and 6.6 mg intravenously on day 8. In arm B, patients received 9.9 mg dexamethasone intravenously on day 1, and 4 mg orally twice daily on days 0 and 2. In arm C, patients received 16.5 mg dexamethasone, 50 mg diphenhydramine, and H_2-blocker intravenously 30 min before the administration of paclitaxel on day 1. They also received 4 mg dexamethasone orally twice daily on days 2 and 3. In arm D, patients received 6.6 mg dexamethasone intravenously on day 1, and 8 mg orally twice daily on days 0 and 2. The use of granulocyte colony-stimulating factor was permitted for treatment of grade 4 neutropenia or febrile neutropenia.

serum concentrations of nivolumab

Serum concentrations of nivolumab were measured by electrochemiluminescence; serum samples were collected on day 1 (before and just before the end of nivolumab infusion), day 8, and day 22 of each cycle or at the end of protocol treatment.

study design

Tolerability was evaluated using the following algorithm. At first, three patients were enrolled in each of the four arms with 10 mg/kg of nivolumab. If dose-limiting toxicity [DLT, adverse events (AEs) defined below] was observed in two or fewer of the three patients, three more patients were enrolled in each arm with 10 mg/kg of nivolumab. If DLT was observed in two or fewer of the six patients, the treatment arm was regarded as tolerable. If DLT was observed in three or more patients, we considered dose reduction of nivolumab to 5 or 2 mg/kg.

The following treatment-related AEs observed during the 3 weeks of the first cycle were defined as DLT: grade 4 neutrophil count decreased, continuing for >7 days; grade 4 febrile neutropenia or grade 3 febrile neutropenia that persists for >24 h; grade 4 thrombocytopenia or grade 3 thrombocytopenia requiring platelet transfusion; non-hematological toxicities of grade 3 or worse; ILD of grade 2 or worse; uncontrollable uveitis, eye pain, or visual acuity reduced of grade 2 or worse; uncontrollable vomiting, anorexia, or diarrhea of grade 3 or worse; intolerable skin toxicities of grade 3 or worse; aminotransferase increased ≥10× the upper limit of normal (ULN), or ≥5× ULN and continuing for >7 days; blood bilirubin increased ≥5× ULN; aminotransferase increased ≥3× ULN and blood bilirubin increased ≥2×

ULN; other grade 4 laboratory abnormalities or grade 3 laboratory abnormalities continuing for >7 days.

AEs were graded on Common Terminology Criteria for AEs (CTCAE) version 4.0. Tumor response was evaluated with computed tomography every 6 weeks according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Objective responses were confirmed by at least one sequential tumor assessment after an interval of 4 weeks or longer.

The study was conducted in accordance with the provisions of the Declaration of Helsinki and with Good Clinical Practice guidelines as defined by the International Conference on Harmonisation, registered with Japanese Pharmaceutical Information Center Clinical Trials Information, number JapicCTI-132071, and approved by the institutional review board. All patients provided written informed consent before enrollment.

results

patients and treatment

From April 2013 through March 2014, six patients in each of the four arms (total 24 patients) were enrolled in this study (Figure 1 and Table 1). Clinical data were collected up to 30 June 2014. The median age was 63 years and 17 patients (70.8%) were male. There were 11 patients (45.8%) with ECOG PS 0 and 13 patients (54.2%) with PS 1. A total of four patients (16.7%, two in arm A and two in arm D) had squamous cell carcinoma. One patient in arm D (4.2%) had NSCLC not otherwise specified, and the others had adenocarcinoma (79.2%). The majority of patients had stage IV disease (70.8%).

As of the data collection cut-off date, 8 of the 24 patients (33.3%) were continuing the study treatment (2 in arm A, 1 in arm B, 5 in arm C, and none in arm D) and all 24 patients survived. Eight patients (two in arm A, two in arm B, one in arm C, and three in arm D) discontinued their study treatments because of disease progression. Two patients (one in arm A and one in arm B) discontinued their study treatments because of treatment delay associated with AEs, and one patient in arm B requested discontinuation of treatment because of AEs. Five patients (one in arm A, one in arm B, and three in arm D) discontinued their study treatments because the investigator judged that the continuous treatment of nivolumab and chemotherapy was not appropriate in consideration of the efficacy or the safety.

In arm A, one patient discontinued cisplatin and gemcitabine at the second cycle, and discontinued nivolumab at the third cycle, but the other five patients completed four cycles of cisplatin, gemcitabine, and nivolumab. In arm B, two patients discontinued at the second and third cycle, respectively, but the other four patients completed four cycles of cisplatin, pemetrexed, and nivolumab. In arm C, two patients discontinued at third cycle, but other four patients completed at least four cycles of carboplatin, paclitaxel, bevacizumab, and nivolumab. In arm D, docetaxel plus nivolumab were administered up to seven cycles (median three cycles). The median follow-up time was 6.23 months (range, 2.04–9.10 months) in arm A, 9.43 months (range, 1.61–11.50 months) in arm B, 7.54 months (range, 5.82–13.90 months) in arm C, and 3.19 months (range, 2.07–5.16) in arm D.

toxicity and tolerability

DLT was observed in only one patient in arm A [alanine aminotransferase (ALT) increased]. Therefore, all four treatment arms were regarded as tolerable. The ALT increased that met definition of DLT resolved with interruption of the protocol treatment and did not required systemic corticosteroid therapy. Hematological AEs of grade 3 or worse were 16.7% in arm A, 16.7% in arm B, 100% in arm C, and 100% in arm D. Non-hematological AEs of grade 3 or worse were 66.7% in arm A, 66.7% in arm B, 0% in arm C, and 50.0% in arm D. There were no treatment-related deaths. Important AEs were reported in Table 2. AEs leading to discontinuation of nivolumab were 33.3% in arm A, 50.0% in arm B, 0% in arm C, and 50.0% in arm D (supplementary Table S1, available at *Annals of Oncology* online). AEs leading to discontinuation of chemotherapy were 16.7% in arm A, 50.0% in arm B, 33.3% in arm C, and 50.0% in arm D (supplementary Table S2, available at *Annals of Oncology* online). Select AEs (those with a potential immunologic cause) are shown in supplementary Table S3, available at *Annals of Oncology* online.

antitumor activity

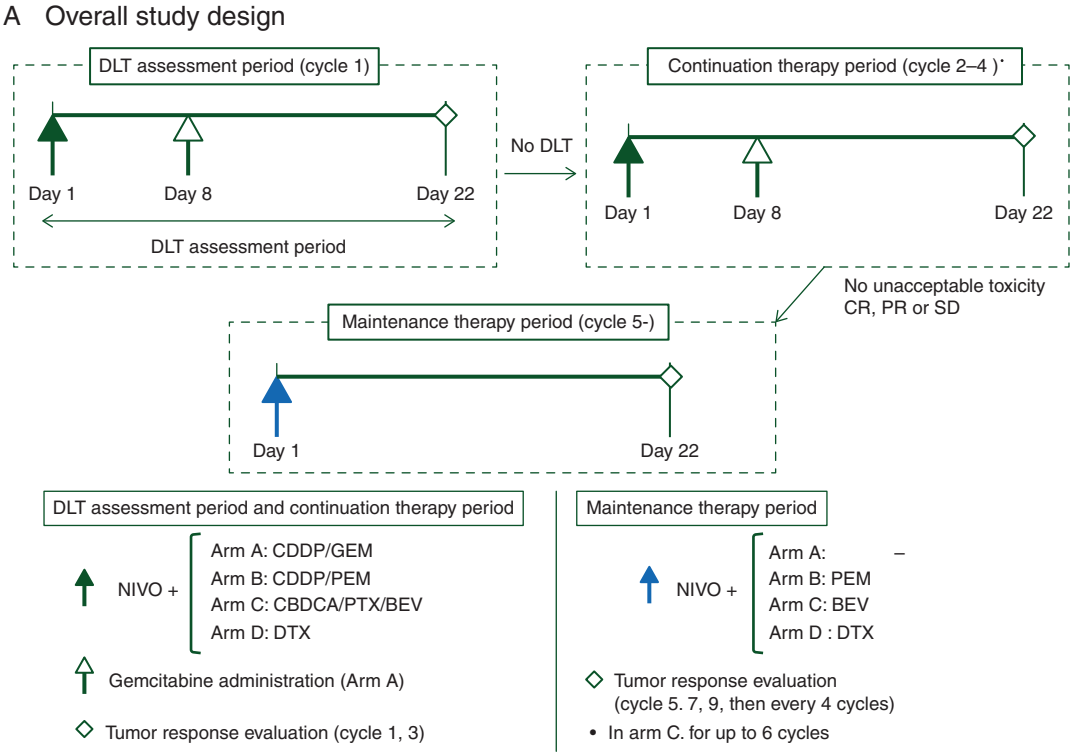
Overall response rates were 50% in arm A, 50% in arm B, 100% in arm C, and 16.7% in arm D. One patient (16.7%) in arm B and one patient (16.7%) in arm D exhibited progressive disease (Table 3 and Figure 2). The median progression-free survival was 6.28 months in arm A, 9.63 months in arm B, not reached in arm C, and 3.15 months in arm D. The median time to response was 2.10 months in arm A, 2.17 months in arm B, 2.14 months in arm C, and 2.04 months in arm D. Eight of the 24 patients (33.3%) were still receiving treatment after the cut-off date (two keeping partial response in arm A, one keeping stable disease in arm B, and five keeping partial response in arm C), and two patients in arm B and one patient in arm D showed continuous response even after discontinuation of study treatment (Figure 3 and supplementary Figure S1, available at *Annals of Oncology* online). We attempted subgroup analysis of objective response by smoking history. The overall response rate was 25.0% with current/former smokers and 100.0% with never-smokers in arm A, 50.0% with current/former smokers and 50.0% with never-smokers in arm B, 100.0% with current/former smokers in arm C, 16.7% with current or former smokers in arm D. There were no never-smokers in arms C and D (supplementary Table S4, available at *Annals of Oncology* online).

serum concentrations of nivolumab

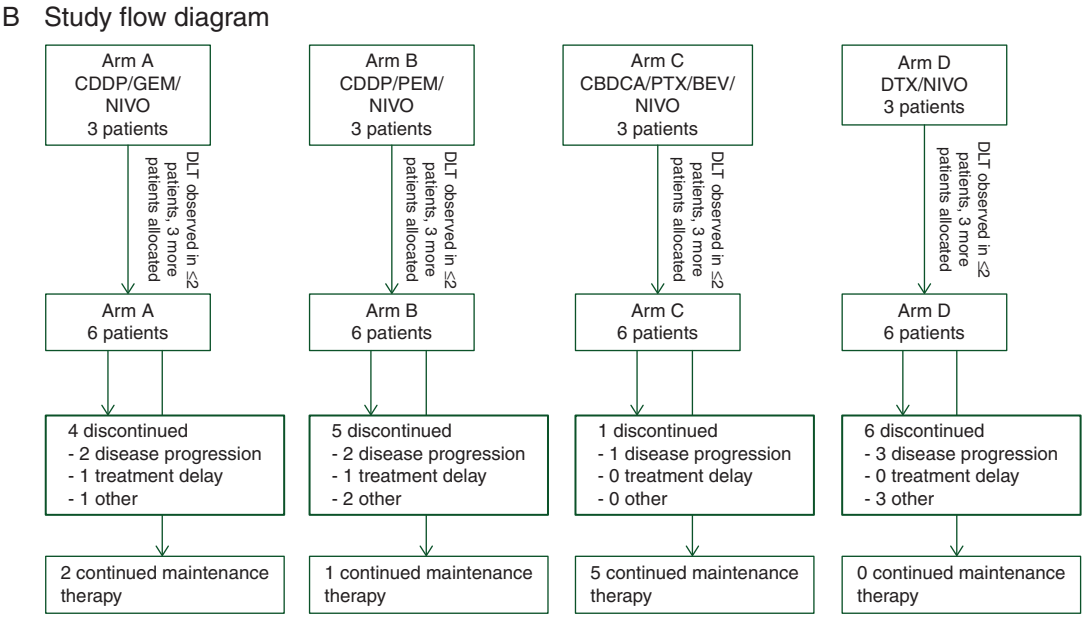
The mean serum concentrations of nivolumab just before the end of nivolumab infusion ranged from 172 to 201 μg/ml on cycle 1 day 1 and the mean trough concentrations ranged from 43 to 54 μg/ml on cycle 1 day 22. The mean serum concentrations of nivolumab just before the end of nivolumab infusion ranged from 255 to 291 μg/ml on cycle 4 day 1 and the mean trough concentrations ranged from 101 to 140 μg/ml on cycle 4 day 22 (Table 3).

discussion

In this phase Ib study, nivolumab 10 mg/kg every 3 weeks plus standard chemotherapy was well tolerated and safe in patients



Abbreviations: DLT, dose limiting toxicity; CDDP, cisplatin; GEM, gemcitabine; NIVO, nivolumab; PEM, pemetrexed; PTX, paclitaxel; BEV, bevacizumab; DTX, docetaxel



Abbreviations: DLT, dose limiting toxicities; CDDP, cisplatin; GEM, gemcitabine; NIVO, nivolumab; PEM, pemetrexed; PTX, paclitaxel: BEV, bevacizumab: DTX, docetaxel

Figure 1. Overall study design (A) and study flow diagram (B).

with advanced NSCLC. DLT was observed in only one patient in arm A (ALT increased). Furthermore, the other AEs observed during the study were acceptable. Although AEs specific to immune checkpoint inhibitors, such as skin toxicities, hepatic toxicities, gastrointestinal toxicities, infusion reaction, pulmonary toxicities endocrine toxicities, and renal toxicities, were observed in some patients, most of these events were grade 1 or 2. In the phase III studies with nivolumab monotherapy (CheckMate 017 study and CheckMate 057 study) [6, 7], rash, aminotransferase increased, diarrhea, infusion-related reaction,

Table 1. Baseline patient characteristics and treatment disposition

Patient characteristics	Total 24	(Arm A) cisplatin gemcitabine nivolumab 6	(Arm B) cisplatin pemetrexed nivolumab 6	(Arm C) carboplatin paclitaxel bevacizumab nivolumab 6	(Arm D) docetaxel nivolumab 6
Age (years)					
Median	63.0	63.0	62.5	64.5	57.0
Range	34–73	58–67	52–73	59–70	34–70
Gender (%)					
Male	17 (70.8)	5 (83.3)	4 (66.7)	4 (66.7)	4 (66.7)
Female	7 (29.2)	1 (16.7)	2 (33.3)	2 (33.3)	2 (33.3)
ECOG PS (%)					
0	11 (45.8)	3 (50.0)	3 (50.0)	2 (33.3)	3 (50.0)
1	13 (54.2)	3 (50.0)	3 (50.0)	4 (66.7)	3 (50.0)
Histology (%)					
Sq	4 (16.7)	2 (33.3)	0 (0.0)	0 (0.0)	2 (33.3)
Ad	19 (79.2)	4 (66.7)	6 (100)	6 (100)	3 (50.0)
NOS	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)
Stage (%)					
IIIB	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)
IV	17 (70.8)	4 (66.7)	5 (83.3)	5 (83.3)	3 (50.0)
Recurrence	6 (25.0)	2 (33.3)	1 (16.7)	1 (16.7)	2 (33.3)
EGFR mutation status					
Negative	16 (66.7)	4 (66.7)	3 (50.0)	6 (100)	3 (50.0)
Positive	4 (16.7)	0 (0.0)	3 (50.0)	0 (0.0)	1 (16.7)
Exon 19 deletion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Exon 21 L858R	2 (8.3)	0 (0.0)	1 (16.7)	0 (0.0)	1 (16.7)
The other mutation	2 (8.3)	0 (0.0)	2 (33.3)	0 (0.0)	0 (0.0)
Unknown	4 (16.7)	2 (33.3)	0 (0.0)	0 (0.0)	2 (33.3)
ALK rearrangement status					
Negative	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)
Positive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Smoking history (%)					
Never smoker	4 (16.7)	2 (33.3)	2 (33.3)	0 (0.0)	0 (0.0)
Previous smoker	19 (79.2)	4 (66.7)	4 (66.7)	5 (83.3)	6 (100)
Current smoker	1 (4.2)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)
Treatment disposition					
Median number of nivolumab administrated (range)		7.5 (3–14)	8.5 (2–15)	11.5 (7–18)	4 (2–7)
Continuing	8 (33.3)	2 (33.3)	1 (16.7)	5 (83.3)	0 (0.0)
Discontinued	16 (66.7)	4 (66.7)	5 (83.3)	1 (16.7)	6 (100)
Disease progression	8 (33.3)	2 (33.3)	2 (33.3)	1 (16.7)	3 (50.0)
Treatment delay	2 (8.3)	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)
Patient request	1 (4.2)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
Physician decision	5 (20.8)	1 (16.7)	1 (16.7)	0 (0.0)	3 (50.0)

ECOG, Eastern Cooperative Oncology Group; PS, performance status; Sq, squamous cell carcinoma; Ad, adenocarcinoma; NOS, not otherwise specified.

pneumonitis, and hypothyroidism of any grade were observed in 4–9%, 2%–3%, 8%, 1%–3%, 3%–5%, and 4%–7% of patients, respectively. In a Japanese phase II study of cisplatin and pemetrexed [14], rash, elevated AST/ALT, and pneumonitis of any grade were observed in 30%, 42%, and 2% of patients, respectively. In a Japanese randomized phase II study of carboplatin, paclitaxel, and bevacizumab (JO19907 study) [15], elevated AST/ALT of any grade were observed in up to 48% of patients. Finally, in a Japanese phase III study of docetaxel (DELTA), rash and elevated AST/ALT of any grade were observed in 15% and up to 24% of patients, respectively [16]. Our results show frequencies of skin toxicities and hepatic toxicities higher than those of chemotherapy or nivolumab alone, but all of these events were mild and did not need intervention with systemic

Table 2. Important adverse events during the study treatment

Events (%)	(Arm A) cisplatin gemcitabine nivolumab		(Arm B) cisplatin pemetrexed nivolumab		(Arm C) carboplatin paclitaxel bevacizumab nivolumab		(Arm D) docetaxel nivolumab	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
All adverse events	6 (100)	4 (66.7)	6 (100)	4 (66.7)	6 (100)	6 (100)	6 (100)	6 (100)
Any hematological adverse events	6 (100)	1 (16.7)	6 (100)	1 (16.7)	6 (100)	6 (100)	6 (100)	6 (100)
White blood cell count decreased	6 (100)		5 (83.3)		6 (100)	3 (50.0)	6 (100)	5 (83.3)
Neutrophil count decreased	6 (100)	1 (16.7)	5 (83.3)	1 (16.7)	6 (100)	6 (100)	6 (100)	6 (100)
Lymphocyte count decreased	4 (66.7)		1 (16.7)		4 (66.7)	1 (16.7)	5 (83.3)	3 (50.0)
Anemia	6 (100)		4 (66.7)		4 (66.7)	1 (16.7)	4 (66.7)	
Platelet count decreased	6 (100)		3 (50.0)		6 (100)	2 (33.3)		
Febrile neutropenia					1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)
Any non-hematological adverse events	6 (100)	4 (66.7)	6 (100)	4 (66.7)	6 (100)		6 (100)	3 (50.0)
Malaise	2 (33.3)		3 (50.0)		3 (50.0)		2 (33.3)	
Pyrexia			1 (16.7)		1 (16.7)		1 (16.7)	
Hypersensitivity	2 (33.3)				1 (16.7)			
Infusion-related reaction					1 (16.7)		2 (33.3)	
Decreased appetite	5 (83.3)	1 (16.7)	5 (83.3)		5 (83.3)		3 (50.0)	1 (16.7)
Nausea	5 (83.3)		4 (66.7)		4 (66.7)		3 (50.0)	
Vomiting	2 (33.3)				1 (16.7)		2 (33.3)	
Diarrhea	1 (16.7)		1 (16.7)		2 (33.3)		1 (16.7)	
Constipation	4 (66.7)		4 (66.7)		4 (66.7)		3 (50.0)	
Stomatitis					2 (33.3)		1 (16.7)	
Blood creatinine increased			1 (16.7)		1 (16.7)			
Blood bilirubin increased	1 (16.7)				1 (16.7)			
ALT increased	3 (50.0)	1 (16.7)	2 (33.3)		3 (50.0)		3 (50.0)	
AST increased	2 (33.3)	1 (16.7)	3 (50.0)		2 (33.3)		3 (50.0)	1 (16.7)
GGT increased	5 (83.3)		4 (66.7)		1 (16.7)		2 (33.3)	1 (16.7)
Hyponatremia	4 (66.7)	2 (33.3)	4 (66.7)	2 (33.3)			2 (33.3)	
Rash			3 (50.0)		3 (50.0)		1 (16.7)	
Rash erythematous			1 (16.7)					
Rash maculo-papular	2 (33.3)				1 (16.7)			
Erythema multiforme			1 (16.7)					
Dry skin			3 (50.0)		2 (33.3)		1 (16.7)	
Pruritus					3 (50.0)		1 (16.7)	
Alopecia	3 (50.0)		1 (16.7)		6 (100)		5 (83.3)	
Epistaxis					4 (66.7)			
Lung infection							1 (16.7)	1 (16.7)
Pneumonia							1 (16.7)	1 (16.7)
Hypoxia							1 (16.7)	1 (16.7)
Interstitial lung disease			2 (33.3)					
Thyroid disorder	1 (16.7)							
Hypothyroidism							1 (16.7)	
Blood thyroid-stimulating hormone decreased							1 (16.7)	
Antithyroid antibody positive							1 (16.7)	
Hypophysitis	1 (16.7)							
Arthralgia					4 (66.7)		1 (16.7)	
Myalgia			1 (16.7)		4 (66.7)		1 (16.7)	
Peripheral sensory neuropathy			1 (16.7)		4 (66.7)		1 (16.7)	
Sensory disturbance			1 (16.7)		2 (33.3)			
Hypoacusis	1 (16.7)	1 (16.7)						
Hypertension	1 (16.7)		1 (16.7)	1 (16.7)	4 (66.7)			
Atrial fibrillation	1 (16.7)	1 (16.7)						
Depression			1 (16.7)	1 (16.7)				

AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyl transpeptidase.

Table 3. Clinical outcomes and serum concentrations of nivolumab

	(Arm A) cisplatin gemcitabine nivolumab	(Arm B) cisplatin pemetrexed nivolumab	(Arm C) carboplatin paclitaxel bevacizumab nivolumab	(Arm D) docetaxel nivolumab
Objective response (%)				
Complete response	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Partial response	3 (50.0)	3 (50.0)	6 (100)	1 (16.7)
Stable disease	2 (33.3)	2 (33.3)	0 (0.0)	3 (50.0)
Progressive disease	0 (0.0)	1 (16.7)	0 (0.0)	1 (16.7)
Not evaluated	1 (16.7)	0 (0.0)	0 (0.0)	1 (16.7)
Overall response rate (%)	50.0	50.0	100	16.7
Time to response (months)[a]				
Median	2.10	2.17	2.14	2.04
Range	0.69–3.55	0.69–2.17	0.69–3.91	2.04
Progression-free survival (months)[a]				
Median	6.28	9.63	Not reached	3.15
Range	0.69[b]–9.10[b]	1.38–11.50[b]	5.26–11.89[b]	0.62[b]–4.80
The rate of PFS at 6 months	60.0	83.3	83.3	0.0
The rate of PFS at 9 months	40.0	83.3	83.3	0.0
Serum concentrations of nivolumab [mean ± SD μg/ml (number of samples)]				
Cycle 1				
Day 1[c]	181 ± 30.7 (6)	179 ± 22.1 (6)	201 ± 50.4 (6)	172 ± 30.1 (6)
Day 22[d]	43 ± 8.3 (5)	47 ± 9.6 (6)	54 ± 11.6 (6)	45 ± 6.9 (6)
Cycle 4				
Day 1[c]	282 ± 33.8 (4)	291 ± 47.9 (4)	279 ± 53.0 (6)	255 ± 12.4 (3)
Day 22[d]	140 ± 41.9 (5)	101 ± 17.4 (4)	114 ± 40.3 (6)	108 ± 7.23 (3)

SD, standard deviation.
[a]Converted at 30.4375 days to 1 month.
[b]Censored data.
[c]Samples were collected just before the end of the nivolumab infusion on day 1 of the cycles.
[d]Samples were collected before administration of nivolumab of the following cycle on day 22.

corticosteroids. ILD was observed in two patients in arm B and occurred several months after the start of the protocol treatment; they were resolved by systemic corticosteroids. These two cases of ILD were different from the early-onset ILD associated with EGFR tyrosine kinase inhibitors. The late-onset of ILD observed in this study is consistent with another clinical study of nivolumab [17] and requires careful monitoring throughout the treatment.

Even though the sample size was limited, this study suggests that combination therapy with nivolumab and standard chemotherapy enhances the antitumor activity of each monotherapy. Overall response rates in all arms (50%–100% in first-line therapy and 16.7% in second-line therapy) were comparable with or higher than those for chemotherapy alone. Furthermore, the median PFS and rates of PFS at 6/9 months of the first-line arms (arms A, B, and C) were better than those for chemotherapy alone. Brief use of corticosteroids for prophylaxis of emesis or allergy was permitted in this study. Although there was concern that immunosuppressive behavior of corticosteroids brought some negative effects to the antitumor activity of nivolumab and combined chemotherapy, these of the combination treatments were favorable. A pooled analysis of nivolumab monotherapy in patients with advanced melanoma also reported that antitumor activities of nivolumab did not wane when immunosuppressive treatment such as corticosteroid was used together [18].

We also investigated serum concentrations of nivolumab in combination with cytotoxic chemotherapy. In the previous Japanese phase I study of nivolumab monotherapy, geometric means of C_{max} and $T_{1/2}$ of nivolumab 10 mg/kg were 192 μg/ml and 21 days, respectively [5]. The trough serum concentrations of nivolumab on cycle 1 day 22 were similar to those of the monotherapy, suggesting that cytotoxic chemotherapy does not influence the serum concentration of nivolumab when the agents are given in combination.

There are several limitations to this study. The sample size of this study was considered reasonable to assess the safety and tolerability of the combination therapy, but was not sufficient to evaluate the clinical efficacy. Furthermore, the optimal dosage and schedule of nivolumab should be reconsidered when planning further study to evaluate the efficacy. Although the administration of 10 mg/kg every 3 weeks was tolerable in this study, there is discrepancy between this studied dose and the approved doses. A biomarker analysis including tumor PD-L1 expression of this study is currently ongoing. Tumor PD-L1 expression are variable factors and it is unclear whether these biomarkers are useful in the setting of a nivolumab and chemotherapy

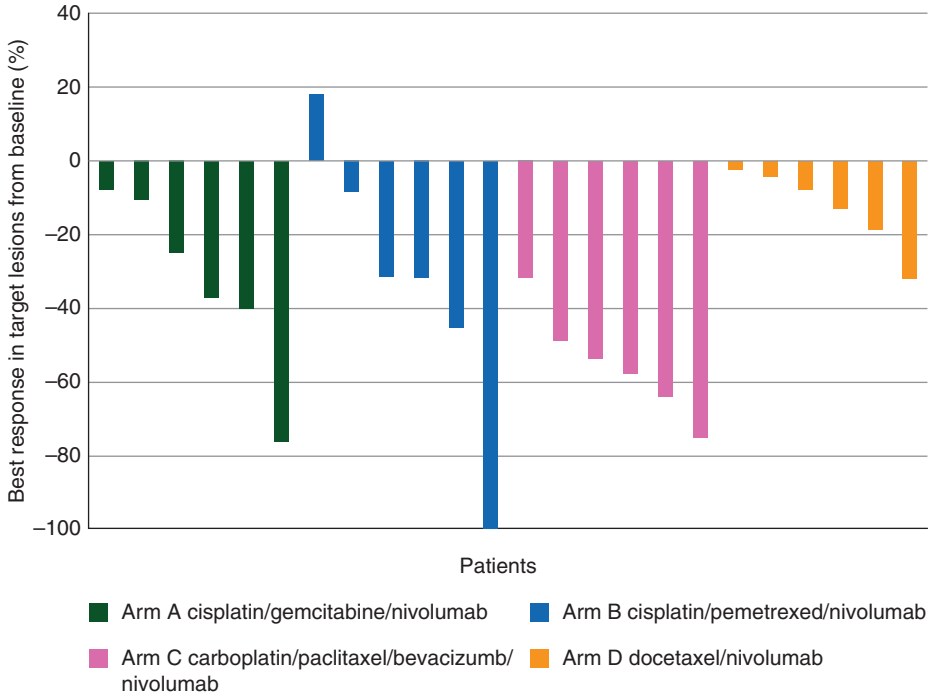


Figure 2. Best response in target lesions from the baseline.

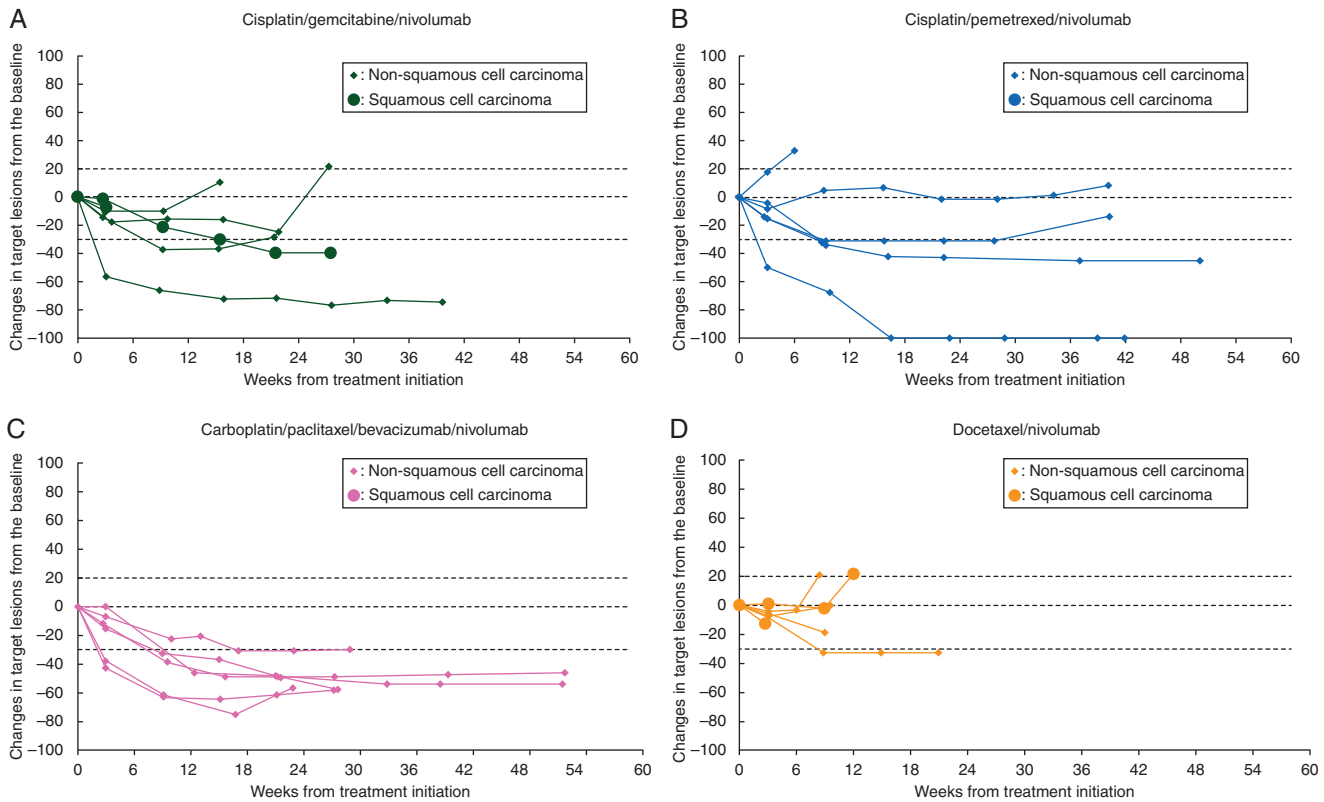


Figure 3. Changes of target lesion from the baseline in patients in arm A (A), arm B (B), arm C (C), and arm D (D).

combination treatment, which may modulate the local immune environment as mentioned above.

In conclusion, this is the one of the few published study on the combination use of nivolumab and standard chemotherapy in patients with advanced NSCLC. This study suggests the safety and encouraging antitumor activity of the combination therapy. Recently, CheckMate 012 study also reported the safety and favorable activity of nivolumab plus platinum-doublet chemotherapy [19]. Further studies to investigate the efficacy and biomarkers of such combination therapy are warranted.

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disclosure

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references

1. Sandler A, Gray R, Perry MC et al. Paclitaxel–carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006; 355: 2542–2550.
2. Scagliotti GV, Parikh P, von Pawel J et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008; 26: 3543–3551.
3. Shepherd FA, Dancey J, Ramlau R et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000; 18: 2095–2103.
4. Topalian SL, Hodi FS, Brahmer JR et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012; 366: 2443–2454.
5. Yamamoto N, Yamada Y, Nokihara H et al. Phase I study of ONO-4538 (BMS-936558), an anti PD-1 antibody, in Japanese patients with advanced solid tumors. Ann Oncol 2012; 23: ix152–ix174.
6. Brahmer J, Reckamp KL, Baas P et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 2015; 373: 123–135.
7. Borghaei H, Paz-Ares L, Horn L et al. Nivolumab versus docetaxel in advanced non-squamous non-small-cell lung cancer. N Engl J Med 2015; 373: 1627–1639.
8. Nowak AK, Robinson BW, Lake RA. Gemcitabine exerts a selective effect on the humoral immune response: implications for combination chemo-immunotherapy. Cancer Res 2002; 62: 2353–2358.
9. Kodumudi KN, Woan K, Gilvary DL et al. A novel chemoimmunomodulating property of docetaxel: suppression of myeloid-derived suppressor cells in tumor bearers. Clin Cancer Res 2010; 16: 4583–4594.
10. Hato SV, Khong A, de Vries IJ et al. Molecular pathways: the immunogenic effects of platinum-based chemotherapeutics. Clin Cancer Res 2014; 20: 2831–2837.
11. Roland CL, Lynn KD, Toombs JE et al. Cytokine levels correlate with immune cell infiltration after anti-VEGF therapy in preclinical mouse models of breast cancer. PLoS One 2009; 4: e7669.
12. Shrimali RK, Yu Z, Theoret MR et al. Antiangiogenic agents can increase lymphocyte infiltration into tumor and enhance the effectiveness of adoptive immunotherapy of cancer. Cancer Res 2010; 70: 6171–6180.
13. Brahmer JR, Drake CG, Wollner I et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol 2010; 28: 3167–3175.
14. Kawano Y, Ohyanagi F, Yanagitani N et al. Pemetrexed and cisplatin for advanced non-squamous non-small cell lung cancer in Japanese patients: phase II study. Anticancer Res 2013; 33: 3327–3333.
15. Niho S, Kunitoh H, Nokihara H et al. Randomized phase II study of first-line carboplatin–paclitaxel with or without bevacizumab in Japanese patients with advanced non-squamous non-small-cell lung cancer. Lung Cancer 2012; 76: 362–367.
16. Kawaguchi T, Ando M, Asami K et al. Randomized phase III trial of erlotinib versus docetaxel as second- or third-line therapy in patients with advanced non-small-cell lung cancer: Docetaxel and Erlotinib Lung Cancer Trial (DELTA). J Clin Oncol 2014; 32: 1902–1908.
17. Nishino M, Sholl LM, Hodi FS et al. Anti-PD-1-related pneumonitis during cancer immunotherapy. N Engl J Med 2015; 373: 288–290.
18. Weber JS, Anotnia SJ, Topalian SL et al. Safety profile of nivolumab (NIVO) in patients (pts) with advanced melanoma (MEL): a pooled analysis. J Clin Oncol 2015; 33(Suppl): 9018.
19. Rizvi NA, Hellmann MD, Brahmer JR et al. Nivolumab in combination with platinum-based doublet chemotherapy for first-line treatment of advanced non-small-cell lung cancer. J Clin Oncol 2016: JCO669861.